REMARKS

In view of the following remarks, the Examiner is requested to allow claims 32, 52, 62-69, 84, 85, 88, 89, 104-107 and 110-113, the only claims pending and under examination in this application.

Formal Matters

Claims 62, 63, 84, 88, 104-107 and 110-113 have been amended to specify that at least two proteins are removed. Support for this amendment can be found in the specification on page 20, lines 13-26, which state:

> The particular proteins to be removed from any one sample are discretionary based on the abundant proteins found in the sample. Different samples can have nearly the same or different abundant proteins that are to be removed. [...]
>
> For a sample where it is unknown which proteins are abundant proteins, one may first do a preliminary separation and analysis to determine the most abundant proteins. Antibodies to these proteins are then generated and used to remove the abundant proteins. The process may be repeated to obtain the desired removal.
>
> The use of such reusable matrices for removing abundant proteins enables the identification and resolution of less abundant proteins in a sample in a reproducible and high throughput fashion. Reproducibility enables comparisons between and among samples. It is preferable to run every sample in a batch or experiment through the same column(s) to control for any variation in immunosubtraction.

Claims 63 and 84 have been amended to specify that each the solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition. Support for this amendment can be found in the specification on page 13, lines 4-7, which state:

> Similar formats to columns include mixing of matrix in a liquid sample whether the matrix is loose beads or in permeable packets, magnetic matrix beads, microarray formats where different receptors are immobilized on

different locations on the matrix(es), liposome or micelle emulsions, dipsticks, tube coatings, etc;

and on page 15, lines 21-28, which state:

> A separate purpose of the instant invention is to provide reagents that can be combined, for removing multiple selected proteins from a sample. Generally, plural proteins are removed from the sample. Thus, a multifunctional matrix that binds a class of proteins or a plurality of individual matrices carrying different agents, such as antibodies of different specificities, are combined. When plural specific matrices are used, the different specific matrices can be mixed in a batch. The mixture can be maintained and used in a batch format or can be loaded into a column. In that case, the different species of matrices can be mixed together.

Claims 63 and 84 have been amended to clarify that the modified sample is not bound by a solid phase matrix. Support for this amendment can be found in the specification on page 27, lines 9-13, which state:

> In the case of serum as a sample, highly glycosylated proteins, about 30% to 50% of the total protein, were bound by the WGA column and separately eluted with a 0.5 M solution of the sugar N-acetylglucosamine, whereas the second fraction consisted of protein unglycosylated or lacking of affinity for this lectin and thus not bound by the column. The gels in Figure 4 visualize the set of proteins from serum unbound (a) or bound and eluted from the lectin affinity column with the sugar (b);

and in the paragraph spanning pages 28-29, which states:

> Serum samples were passed over the column. Sample volumes generally were less than 100 µl in volume. The proteins were washed through with neutral buffer. The eluate was obtained, concentrated and then the proteins therein were separated by 2-DGE. The gels were stained with Coomassie blue and silver stains to reveal the less abundant proteins of serum

as exemplary locations.

The remaining amendments to the claims are made for clarity and to make sure that, where appropriate, dependent claims terms have appropriate and clear antecedent basis, to correct typographical errors, and to correct errant dependencies.

As no new matter has been added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Claim Rejections – 35 U.S.C. § 112

Claims 32, 52, 62-69, 84, 85, 88, 89, 104-107 and 110-113 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Telephonic interview: The Examiner was contacted by telephone in order to ascertain the status of amendments to Claims 63 and 84, "specific predefined **ligands** ~~proteins~~," which appeared not to have been acknowledged in the Examiner's response (Office Action, page 3). The Examiner responded by telephone that the relevant sentences were written in error and should reflect the amendment to the claims. Accordingly, page 3 of the Office Action is herein interpreted to read "specific predefined ligands," as applies to the instant claims. The Examiner is thanked for the clarification.

Following entry of the above amendments, Claim 63 reads:

63. A method for producing a modified sample, said method comprising:

removing at least a first protein and a second protein from a sample, said removing step comprising contacting said sample with an affinity binding composition comprising a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to said first protein but not said second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to said second protein but not said first protein, wherein each said

solid phase matrix is a plurality of particles and said first and second solid phase matrices are present as a mixture in said binding composition,

so that when said sample is contacted with said affinity binding composition, said first protein present in said sample binds to said first receptor present on said first solid phase matrix such that said first protein is removed from said sample and said second protein present in said sample binds to said second receptor present on said second solid phase matrix such that said second protein is removed from said sample and said modified sample is thereby produced, wherein said modified sample is not bound by a solid phase matrix; and

recovering said modified sample.

Claim 84 reads in a similar fashion.

In maintaining this rejection, the Examiner alleges that the recitation of "specific predefined proteins" is indefinite.

Without in any way agreeing with the position of the Office and solely in order to expedite prosecution of the application, the Applicants have amended Claims 63 and 84 to remove the assertedly indefinite language and as such respectfully request withdrawal of the rejection.

The Examiner further alleges that type mismatches between the terms "first protein present in the sample," "second protein present in the sample," and "such that the first and second proteins are removed" render Claim 63 indefinite.

Without in any way agreeing with the position of the Office and solely in order to expedite prosecution of the application, the Applicants have amended Claim 63 to remove the assertedly indefinite language and as such respectfully request withdrawal of the rejection.

The Examiner further alleges that the type mismatch "ligands become bound[...] and thereby removed" in Claim 84 renders the claims indefinite.

Without in any way agreeing with the position of the Office and solely in order to expedite prosecution of the application, the Applicants have amended Claim 84 to remove the assertedly indefinite language and as such respectfully request withdrawal of the rejection.

The Examiner further alleges that the phrase "each solid phase matrix comprises a plurality of particles" in Claims 63 and 84 is indefinite, wherein "each solid phase matrix" = a bead (specification, page 9, lines 10-11), since whether or how a bead comprises "a plurality of particles" is not clear.

Without in any way agreeing with the position of the Office and solely to expedite prosecution of the application, the Applicants have amended Claims 63 and 84 to clarify the assertedly indefinite language and as such respectfully request withdrawal of the rejection.

The Examiner further asserts that the phrases "a first and second solid phase matrix contacting each other" in Claim 63 and "each solid phase matrix is in contact with at least one other solid phase matrix" in Claim 84 are indefinite, wherein "each solid phase matrix" = beads (specification, page 13, lines 4-7), since whether or how a matrix of beads is in contact with another matrix of beads is not clear, and how the same can be "present as a mixture" is not clear.

Without in any way agreeing with the position of the Office and solely to expedite prosecution of the application, the Applicants have amended Claims 63 and 84 to clarify the assertedly indefinite language.

Further, the dictionary definition of "mixture" in the Merriam-Webster Online Dictionary (accessible by entering the URL http(colon)//www(dot)m-w(dot)com/dictionary/mixture into the appropriate field of a browser) is:

1 (a) : the act, the process, or an instance of mixing (b) (1) : the state of being mixed (2) : the relative proportions of constituents; especially : the proportion of fuel to air produced in a carburetor

2 : a product of mixing : combination: as (a) : a portion of matter consisting of two or more components in varying proportions that retain their own properties (b) : a fabric woven of variously colored threads (c) : a combination of several different kinds.

As such, the Applicants submit that the term "mixture" is plain English, and the term as it is commonly used makes the limitations of the instant claim very clear to the ordinarily skilled artisan in the relevant field. The Applicants respectfully submit that the alternative interpretations of "mixture" offered by the Examiner, namely, that of "stacked, layered and/or adjoined" have no foundation in the claims language or the specification. The Applicants respectfully point out that a set of items arranged in a stack, as layers, or adjoined are by definition not arranged as a mixture.

In view of the foregoing discussion, it is believed that the rejection has been adequately addressed. Withdrawal of the rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 102

Claims 32, 52, 62-69, 89, 104, 110 and 112 are rejected under 35 U.S.C. 102(b) as being anticipated by Stausbøl-Grøn *et al.*, 391 FEBS Letters 71 (1996).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The instant claims are directed to, *inter alia*, a method for producing a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition so that when the sample is contacted with the affinity

binding composition, the first protein present in the sample binds to the first receptor present on the first solid phase matrix such that the first protein is removed from the sample and the second protein present in the sample binds to the second receptor present on the second solid phase matrix such that the second protein is removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample. It is not seen where this is taught in Stausbøl-Grøn *et al.*

The Examiner defines the step of removing in Stausbøl-Grøn *et al.* as:

> (1) removing (see p. 72, col. 1, fifth paragraph, "immunobead was washed") at least two specific predefined proteins (see p. 73, col. 2, second paragraph, "Competitive proteins", see Fig. 2(A), MIX+LDH versus MIX; see also Section 3 Results and discussion, p. 74, right column, second full paragraph, first sentence, "selection inhibition of all similarities"; see also last sentence, "as many proteins as possible") (emphasizing plurality of proteins) from a sample that contains the at least two specific predefined proteins (Office Action, page 3-4)

Since the alleged step of removing in Stausbøl-Grøn *et al.* involves washing excess competitive proteins away from the proteins that are bound to the immunobead, as cited by the Examiner, Stausbøl-Grøn *et al.* fail to teach that the modified sample is not bound by a solid phase matrix (e.g., immunobead), as is claimed.

Accordingly, Stausbøl-Grøn *et al.* fail to teach each and every limitation of the claims.

The rejection may be withdrawn for this reason alone.

Moreover, in the removing step of Stausbøl-Grøn *et al.* as defined by the Examiner, the modified sample is produced by removing (i.e., washing away) the "competitive proteins," "mix" etc. from the solid phase matrix, in contradistinction to

binding of the "competitive proteins," "mix" etc. to the bead. This fails to meet the limitations of the claims, which recite that the first protein present in the sample binds to the first receptor present on the first solid phase matrix such that the first protein is removed from the sample and the second protein present in the sample binds to the second receptor present on the second solid phase matrix such that the second protein is removed from the sample and the modified sample is thereby produced. In contradistinction, Stausbøl-Grøn *et al.* teach that the modified sample is produced on the bead when the excess protein is washed away.

Accordingly, since Stausbøl-Grøn *et al.* fail to teach at least these elements of the claims, Claims 32, 52, 62-69, 89, 104, 110 and 112 are not anticipated under 35 U.S.C. 102(b) by Stausbøl-Grøn *et al.* Withdrawal of the rejection is respectfully requested.

Claims 32, 52, 62, 84, 89, 104, 111 and 113 are rejected under 35 U.S.C. 102(b) as being anticipated by Stausbøl-Grøn *et al.*, 391 FEBS Letters 71 (1996).

The instant claims are directed to, *inter alia*, a method for producing a modified sample, the method including contacting the sample with an affinity binding composition including a plurality of solid phase matrices with a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity, in which each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition. It is not seen where this is taught in Stausbøl-Grøn *et al.*

Arguments made above regarding Claims 32, 52, 62, 89 and 104 are reiterated as applied to the instant rejection. The rejection may be withdrawn for the above-stated reasons alone.

Moreover, in maintaining the rejection, the Examiner defines the asserted "affinity binding composition" as being the "single-chain Fv antibody fragments (scFV)" of Stausbøl-Grøn *et al.* (Office Action, page 10).

The Examiner further defines the asserted "plurality of solid phase matrices," as being the "naïve phagemid library" of Stausbøl-Grøn *et al.* (Office Action, page 10).

However, the Applicants respectfully point out that "single-chain Fv antibody fragments (scFV)" do not comprise a "naïve phagemid library." Since the instant claims recite an affinity binding composition comprising a plurality of solid phase matrices, the teachings of Stausbøl-Grøn *et al.* additionally fail to meet this limitation of the claims.

Moreover, as discussed above, the Examiner defines the asserted "plurality of solid phase matrices" as being the "naïve phagemid library" of Stausbøl-Grøn *et al.* (Office Action, page 10).

The Examiner further defines the asserted "plurality of particles" as being the "coat protein" of Stausbøl-Grøn *et al.* (Office Action, page 11).

However, the Applicants respectfully point out that each "naïve phagemid library" is not a "coat protein." Since the instant claims recite that each solid phase matrix is a plurality of particles, the teachings of Stausbøl-Grøn *et al.* additionally fail to meet this limitation of the claims.

Accordingly, since Stausbøl-Grøn *et al.* fail to teach at least these elements of the claims, Claims 32, 52, 62, 84, 89, 104, 111 and 113 are not anticipated under 35 U.S.C. 102(b) by Stausbøl-Grøn *et al.* Withdrawal of the rejection is respectfully requested.

Claims 32, 52, 62-69, 84, 88-89, 104 and 110-113 are rejected under 35 U.S.C. 102(e) as being anticipated by Payan (US 6,455,263).

The instant claims are directed to, *inter alia*, a method for producing a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition so that when the sample is contacted with the affinity binding composition, the first protein present in the sample binds to the first receptor present on the first solid phase matrix such that the first protein is removed from the sample and the second protein present in the sample binds to the second receptor present on the second solid phase matrix such that the second protein is removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample. It is not seen where this is taught in Payan.

The Examiner defines the asserted steps of removing and recovering in Payan as:

> (1) removing at least two 'specific predefined proteins (see *e.g.*, col. 13, lines 10-1 1, "nonfluorescent beads") from a sample that contains the at least two specific predefined proteins (see e.g., col. 3, lines 48-49, "library of candidate agents"; col. 14, lines 24-25, "third, fourth, etc. populations of target molecules"), thereby producing a modified sample containing a plurality of proteins (see col. 13, lines 10-1 1, "sorting results in a population of nonfluorescent beads and at least one population of fluorescent beads")
>
> (2) recovering the modified sample (see col. 2, lines 64-65, "collected") (Office Action, page 12).

Since the alleged step of removing in Payan involves separating the beads which are bound to the modified sample from beads which are not, as cited by the Examiner (col. 13, lines 10-1 1, "sorting results in a population of nonfluorescent beads and at least one population of fluorescent beads"), Payan fails to teach that

the modified sample is not bound by a solid phase matrix (e.g., fluorescent or nonfluorescent bead), as is claimed.

Accordingly, since Payan fails to teach at least this element of the claims, Claims 32, 52, 62-69, 84, 88-89, 104 and 110-113 are not anticipated under 35 U.S.C. 102(e) by Payan. Withdrawal of the rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 32, 52, 62-69, 84-85, 88-89, 104-107 and 110-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davies (US 6,696,304) in view of Payan (US 6,455,263).

To establish a *prima facie* case of obviousness, the prior art reference, or references when combined, must teach or suggest all the claim limitations. *In re Royk*a, 180 USPQ 580 (CCPA 1974).

The instant claims are directed to, *inter alia*, a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein (Claim 63), or a plurality of solid phase matrices with a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity (Claim 84). It is not seen where either is taught in Davies.

The Examiner cites a plurality of receptors immobilized on the plurality of solid phase matrices (see e.g., col. 14, line 52, "antibody") (Office Action, page 15). However, this does not exhaust the limitations of the instant claims, which are directed to receptors capable of specific binding to particular proteins, such that each has a different protein binding specificity.

Davies assertedly teaches a standard for a protein assay consisting of a mixture of proteins where each protein should be bound to a distinguishable bead; however, Davies does not teach binding specificity to a protein.

In discussing classes of proteins which may be used as reference substances, Davies refers generically to Ig molecules. Davies nowhere teaches that the Ig molecules specifically bind to different proteins, since the identity of the different Ig molecules is not relevant to the invention of Davies.

One of skill in the art understands that the binding specificity of the reference proteins of Davies is unimportant to the assay and, as such, the artisan could for example choose (a) to use different Ig isotypes all of which specifically bind to the same protein, (b) Ig Fc domains of different isotypes, which bind to no protein, (c) molecules with no identified binding specificity whatsoever, etc. As such, the ordinarily skilled artisan would find no guidance in Davies towards arriving at the instant claims.

The Applicants therefore submit that Davies fails to teach or suggest at least this element of the claims.

Moreover, Davies further fails to teach removing at least two specific predefined proteins from a sample, producing a modified sample, and recovering the modified sample, as acknowledged by the Examiner (Office Action, page 15).

Accordingly, since Davies fails to teach the claimed removing, producing and recovering, Davies additionally fails to teach that the modified sample is not bound by a solid phase matrix, as is claimed.

In seeking to remedy these deficiencies in Davies, the Examiner turns to Payan. As established above, Payan fails to teach that the modified sample is not bound by a solid phase matrix (e.g., fluorescent or nonfluorescent bead), as is claimed. As such, Payan fails to remedy this and other deficiency in Davies.

Moreover, the method of Payan depends upon using FACS to isolate fluorescent beads which constitute the modified sample (i.e., Payan, column 1, lines 50-53, "The presence of at least one fluorescent bead is indicative that at least one candidate bioactive agent that binds to at least one target molecule.") As such, one of skill in the art finds no guidance in Payan towards arriving at a method in which the modified sample is not bound by a solid phase matrix, as is claimed. Payan therefore fails to teach, or even to suggest, this limitation of the claims.

As such, the combined references, taken separately or together, fail to teach or suggest multiple elements of the claims. Accordingly, for at least these reasons Claims 32, 52, 62-69, 84-85, 88-89, 104-107 and 110-113 are patentable under 35 U.S.C. 103(a) over Davies (US 6,696,304) in view of Payan (US 6,455,263). Withdrawal of the rejection is respectfully requested.

Claims 32, 52, 62-69, 84-85, 88-89, 104-107 and 110-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davies (US 6,696,304) in view of Fulwyler *et al.* (US 3,710,933).

In making this rejection the Examiner asserts that Davies teaches each and every element of the claims with the exception of the steps of removing at least two specific predefined proteins from a sample, producing a modified sample and recovering the modified sample, for which elements the Examiner turns to Fulwyler *et al.*

Fulwyler *et al.* assertedly "describes a particle sorter (see Title) for sorting stuff."

As established above, Davies nowhere teaches or suggests a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein (Claim 63), or a plurality of solid phase matrices with a plurality of

receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity (Claim 84).

As further established above, Davies additionally fails to teach or to suggest that the modified sample is not bound by a solid phase matrix, as is claimed.

Since Fulwyler *et al.* was cited solely for a sorter, it fails to remedy these deficiencies in Davies, since one of skill in the art understands a sorter to utilize binding to solid phase matrices to isolate samples.

Accordingly, for at least these reasons Claims 32, 52, 62-69, 84-85, 88-89, 104-107 and 110-113 are patentable under 35 U.S.C. 103(a) over Davies (US 6,696,304) in view of Fulwyler *et al.* (US 3,710,933). Withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 327-3400.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10030634-2.

Respectfully submitted,

Date: July 3, 2007

By: _____
Bret E. Field
Registration No. 37,620

AGILENT TECHNOLOGIES, INC.
Legal Department, DL429
Intellectual Property Administration
P.O. Box 7599
Loveland, CO 80537-0599

F:\DOCUMENT\AGIL\401CON (10030634-2)\10030634-2 (AGIL-401CON) Response to OA dtd 4-3-07.doc